Angiotensin Modulator Combinations
Therapeutic Class Review (TCR)

December 16, 2016

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
amlodipine / benazepril (Lotrel®)[1]	generic, Novartis	Hypertension (not as initial therapy)
amlodipine / olmesartan (Azor®)[2]	generic, Daiichi Sankyo	Treatment of hypertension either alone or in combination with other agents Initial therapy in patients likely to need multiple antihypertensive agents to achieve their blood pressure goals
amlodipine / olmesartan / HCTZ (Tribenzor®)[3]	generic, Daiichi Sankyo	Hypertension (not as initial therapy)
amlodipine / perindopril (Prestalia®)[4]	Symplmed	Treatment of hypertension for patients not adequately controlled on monotherapy Initial treatment of hypertension in patients who will likely require multiple medications for blood pressure control
amlodipine / telmisartan (Twynsta®)[5]	generic, Boehringer Ingelheim	Treatment of hypertension alone or in combination with other agents Initial treatment of hypertension in patients who will likely require multiple medications for blood pressure control
amlodipine / valsartan (Exforge®)[6]	generic, Novartis	Initial treatment of hypertension in patients who will likely require multiple medications for blood pressure control Treatment of hypertension for patients not adequately controlled on monotherapy
amlodipine / valsartan / HCTZ (Exforge HCT®)[7]	generic, Novartis	Hypertension (not initial therapy)
nebivolol / valsartan (Byvalson)[8]	Allergan	Hypertension, as initial therapy and in patients not adequately controlled on the individual components
verapamil SR / trandolapril (Tarka®)[9]	generic, Abbott	Hypertension (not as initial therapy)

HCTZ = hydrochlorothiazide

OVERVIEW

Approximately 80 million adults in the United States have hypertension.[10] Hypertension is an independent risk factor for cardiovascular disease, and antihypertensive treatment lowers the risk of cardiovascular disease. The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) treatment algorithm for hypertension includes combination therapy as a therapeutic option.[11] Most hypertensive patients require at least 2 medications to achieve adequate blood pressure (BP) reduction as seen in a large clinical trial.[12]

PHARMACOLOGY[13,14,15,16,17,18]

These agents are a fixed-dose combination of 2 or 3 of the following: an angiotensin II receptor blocker (ARB) or an angiotensin-converting enzyme (ACE) inhibitor in combination with a calcium channel blocker (CCB) or a beta blocker, with or without the addition of a thiazide diuretic.

ACE inhibitors included in this class of combination products include benazepril, perindopril, and trandolapril, components of Lotrel, Prestalia, and Tarka, respectively.

ACE inhibitors prevent the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, by competing with angiotensin I for the active site of ACE. The reduction of angiotensin II formation decreases vasoconstriction, decreases aldosterone secretion, and increases plasma renin. This causes a reduction in blood pressure and total peripheral resistance, and decreased sodium and water retention. There is also a possible local action within the vascular wall that is responsible for blood pressure reduction.

Azor, Twynsta, and Exforge contain olmesartan, telmisartan, and valsartan, respectively, which are angiotensin II receptor blockers. Angiotensin II causes vasoconstriction, release of aldosterone and antidiuretic hormone, sympathetic activation, and constriction of the efferent arterioles of the glomerulus in the kidneys. ARBs block the vasoconstrictive and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, such as vascular smooth muscle and the adrenal gland. Non-ACE pathways also produce angiotensin II. ARBs do not inhibit ACE (kinase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin), nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Calcium channel blockers inhibit calcium ions from moving across the cell membrane. The limitation of calcium entering into the cells causes a decrease in mechanical contraction of myocardial and smooth muscle, thereby causing dilation of systemic arteries and a decrease in total peripheral resistance, systemic blood pressure, and the afterload of the heart. The dihydropyridine CCB amlodipine (a component of Lotrel, Azor, Tribenzor, Prestalia, Twynsta, Exforge, and Exforge HCT) is a potent vasodilator and can increase or have a neutral effect on vascular permeability. The nondihydropyridine CCB verapamil (a component of Tarka) is a potent vasodilator, but verapamil has a greater depressive effect on cardiac conduction and contractility.

Hydrochlorothiazide (HCTZ; a component of Tribenzor and Exforge HCT) is a thiazide diuretic that exhibits its pharmacological effects by blocking the reabsorption of sodium and chloride leading to diuresis and a reduction in intravascular volume. Concurrent administration of an angiotensin II receptor antagonist, such as valsartan, and a thiazide diuretic may help to decrease potassium loss that occurs with thiazide diuretic therapy.

Nebivolol, a component of Byvalson, is a beta-adrenergic receptor blocking agent that also has a direct vasodilatory effect. It is primarily β1 selective at doses under 10 mg for the majority of the population, which consists of extensive metabolizers. In high doses and in poor metabolizers, nebivolol exhibits both β1 and β2 adrenergic receptor inhibition. Nebivolol does not exert any α1 adrenergic receptor blocking activity. Its antihypertensive response may be attributed to decreased heart rate and myocardial contractility; diminished peripheral sympathetic outflow from cerebral vasomotor centers; suppression of renin activity; and reduced peripheral vascular resistance and vasodilation.

Blood pressure is lowered through the antihypertensive mechanisms of all components of the combinations.

PHARMACOKINETICS[19,20,21,22,23,24,25,26,27,28,29]

There are no pharmacokinetic profile changes with combination products versus each single agent, except with verapamil SR 240 mg and trandolapril 4 mg (Tarka), in which an increase in area under the curve (AUC) and maximum serum concentration (Cmax) are seen with verapamil.

Brand Name	Generic Name	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion (%)
Lotrel	amlodipine	64-90	~48	extensively metabolized	Urine: 70
	benazepril	> 37	10-11	benazeprilat (~100%)	Primarily urine
Azor	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	olmesartan	26	13	none significant	Feces: 50-65 Urine: 35-50
Tribenzor	amlodipine	64-90	30-50	extensively metabolized	Urine: 55
	olmesartan	26	13	none significant	Feces: 50-65 Urine: 35-50
	hydrochlorothiazide	--	5.6-14.8	not metabolized	Urine: 61
Prestalia	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	perindopril	75 (as perindopril)	1.3	perindoprilat	Urine: 75 Feces: 25
Twynsta	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	telmisartan	42-58	24	metabolized to glucuronide conjugate	Feces: > 97
Exforge	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	valsartan	25	6	20% of dose converted to metabolites	Urine: 13 Feces: 83
Exforge HCT	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	hydrochlorothiazide	--	5.8-18.9	not metabolized	Urine: 61
	valsartan	10-35	6	20% of dose converted to metabolites	Urine: 13 Feces: 83
Byvalson	nebivolol	undetermined	12-19	mainly direct glucuronidation and secondarily via N-dealkylation and oxidation via CYP2D6	Urine: 38-67 Feces: 13-44
	valsartan	10-35	6	20% of dose converted to metabolites	Urine: 13 Feces: 83
Tarka	trandolapril	10 (as trandolapril)	10	trandolaprilat	Urine: 33 Feces: 66
	verapamil SR	20-35	6-11	12 metabolites; norverapamil is 20% as potent as parent	Urine: 70 Feces: 16

CONTRAINDICATIONS/WARNINGS[30,31,32,33,34,35,36,37,38]

All product labeling for agents in this review contain boxed warnings regarding the use of drugs that act directly on the renin-angiotensin-aldosterone system during pregnancy can cause fetal and neonatal morbidity and death and, when pregnancy is detected, should be discontinued as soon as possible.

Angioedema of the head and neck can occur with any angiotensin modulating agent. If angioedema involves the tongue or airway, respiratory distress may occur and could result in death without prompt treatment. Verapamil SR/trandolapril (Tarka) is contraindicated in patients with a history of angioedema related to previous ACE Inhibitor therapy. Amlodipine/benazepril (Lotrel) and amlodipine/perindopril (Prestalia) use is contraindicated in patients with a history of angioedema regardless of previous ACE Inhibitor use.

Hypersensitivity to any of these products is considered a contraindication.

Renal function should be monitored periodically. Changes in renal function, including acute renal failure, can be caused by drugs that affect the renin-angiotensin system. In patients who develop a clinically significant decrease in renal function, withholding or discontinuing therapy should be considered.

Dual blockade of the renin-angiotensin-aldosterone system is associated with increased risk of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure). Closely monitor blood pressure, renal function, and electrolytes in patients on ACE inhibitors and ARBs.

In both the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) and Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT) trials, patients with type 2 diabetes were given either olmesartan or placebo to determine if treatment with olmesartan would slow the progression of kidney disease. An unexpected finding observed in both trials was a greater number of deaths from a cardiovascular cause (MI, sudden death, or stroke) in the olmesartan-treated patients compared to placebo. The Food and Drug Administration (FDA) has completed its safety review in which patients with type 2 diabetes were taking olmesartan (Benicar) and found no clear evidence of a higher rate of cardiovascular risk as compared to placebo.[39] The FDA reminds practitioners that numerous clinical trials with olmesartan, as well as trials with other ARBs, have not suggested an increased risk of cardiovascular-related death. Currently, the FDA still believes that the benefits of olmesartan in patients with hypertension continue to outweigh the potential risks.

Sprue-like enteropathy has been reported in patients taking olmesartan months to years after the start of the drug. Severe chronic diarrhea with substantial weight loss has been reported and, if a patient develops these symptoms while on olmesartan, other etiologies must be excluded. Stopping olmesartan therapy in cases where no other etiologies are identified should be considered.

Beta-blockers such as nebivolol (contained in Byvalson) may mask tachycardia a typical clinical sign of hypoglycemia and hyperthyroidism. In patients with coronary artery disease, Byvalson must not be abruptly discontinued as this could lead to worsening of angina, myocardial infarction and ventricular arrhythmias.

In July 2010, the FDA announced that they were conducting a review of ARBs after a meta-analysis including data from over 60,000 patients suggested that ARBs may be associated with a small increased risk of cancer.[40] In June 2011, the FDA concluded that treatment with an ARB does not increase cancer

risk.[41] To draw this conclusion, the FDA conducted a trial-level meta-analysis of 31 clinical trials in which patients were randomized to treatment with an ARB (n=84,461) or a non-ARB (n=71,355). The meta-analysis evaluated the association between ARBs and the risk of incident (new) cancer, cancer-related death, breast cancer, lung cancer, and prostate cancer. The rate of cancer events in the ARB group was 1.82 per 100 patient-years compared to 1.84 per 100 patient-years in non-ARB comparators. The relative risk of cancer in patients taking ARBs was 0.99 (95% confidence interval [CI], 0.92 to 1.06). The FDA also found no evidence of association between ARBs and cancer-related death (relative risk [RR], 1.04; 95% CI, 0.96 to 1.13), breast cancer (odds ratio [OR], 1.06; 95% CI, 0.9 to 1.23), lung cancer (OR, 1.07; 95% CI, 0.89 to 1.29), or prostate cancer (OR, 1.05; 95% CI, 0.95 to 1.17). In 2011, another meta-analysis assessed the association between antihypertensive drugs and cancer risk.[42] It included 70 randomized controlled trials with 324,168 participants and recorded no difference in the risk of cancer with ARBs. There was an increased risk with the combination of ACE Inhibitors plus ARBs (2.3%; OR, 1.14; 95% CI, 1.02 to 1.28); however, this risk was not apparent in the random-effects model (OR, 1.15; 95% CI, 0.92 to 1.38).

Due to the verapamil component, verapamil SR/trandolapril (Tarka) is contraindicated in patients with severe left ventricular dysfunction (LVD), hypotension (systolic blood pressure [SBP] < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker), second or third degree AV block (except in patients with a functioning artificial ventricular pacemaker), atrial flutter or atrial fibrillation, and an accessory bypass tract (e.g., Wolff-Parkinson-White, Lown-Ganong-Levine syndromes).

Amlodipine/valsartan/HCTZ (Exforge HCT) and amlodipine/olmesartan/HCTZ (Tribenzor) are contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs due to the hydrochlorothiazide component. Thiazide diuretics may also cause exacerbation or activation of systemic lupus erythematosus. The potential exists for electrolyte (e.g., hypercalcemia, hypochloremic alkalosis, hypokalemia, hypomagnesemia, hyponatremia, and hyperuricemia) or fluid imbalances; monitoring is recommended.

Hydrochlorothiazide can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms, such as acute onset of decreased visual acuity or ocular pain, can occur within hours to weeks of drug initiation. If untreated, acute angle-closure glaucoma can lead to permanent vision loss. Hydrochlorothiazide should be discontinued as rapidly as possible. Prompt medical or surgical treatments may be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Worsening angina and acute myocardial infarction may develop after beginning or increasing the dose of amlodipine, especially in patients with severe obstructive coronary artery disease.

Appropriate caution is necessary when using amlodipine in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Olmesartan, one of the components of Azor and Tribenzor, can cause hyperkalemia as it is an inhibitor of the renin-angiotensin system. Therefore, serum electrolytes must be monitored regularly.

Nebivolol/valsartan (Byvalson) is contraindicated in patients with severe bradycardia, heart block (> first degree), decompensated heart failure, severe hepatic impairment, sick sinus syndrome and cardiogenic shock. In patients with diabetes, Byvalson should not be given concurrently with aliskiren.

DRUG INTERACTIONS[43,44,45,46,47,48,49,50,51]

ACE inhibitors interact with azathioprine, cyclosporine, lithium, nonsteroidal anti-inflammatory drugs (NSAIDs), potassium sparing diuretics, trimethoprim, and eplerenone (Inspra®). Concurrent use of loop and thiazide diuretics can increase the risk of hypovolemia and increase the risk of nephrotoxicity.

The risk of angioedema may be increased with concurrent use of ACE inhibitors and mammalian target of rapamycin (mTOR) inhibitors. Increases in serum lithium concentrations and lithium toxicity have been reported with concurrent use of lithium and ARBs. Serum lithium levels should be monitored with concurrent use. Verapamil can interact with digoxin, lithium, erythromycin, clarithromycin, beta-blockers, carbamazepine, rifampin, phenobarbital, cyclosporine, theophylline, and select antiarrhythmic agents.

In elderly volume-depleted (including those on diuretic therapy) or renally-compromised patients, co-administration of NSAIDs, including selective COX-2 inhibitors, with agents acting on the renin-angiotensin system (ACE inhibitors, ARBs) may result in decreased renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving ACE inhibitors or ARBs, with NSAID therapy. In addition, the antihypertensive effect of ACE inhibitors and ARBs may be reduced by NSAIDs, including selective COX-2 inhibitors.

Co-administration of multiple doses of amlodipine or verapamil with 80 mg simvastatin may result in a significant increase in exposure to simvastatin. Simvastatin dose should not exceed 20 mg per day in patients on amlodipine. For patients on verapamil, limit the dose of simvastatin to 10 mg daily and the dose of lovastatin to 40 mg. Lower starting and maintenance doses of other CYP3A4 substrates (e.g., atorvastatin) may be required as verapamil may increase the plasma concentration of these drugs.

Concomitant use of verapamil and ivabradine may increase exposure to ivabradine and lead to exacerbation of bradycardia and conduction disturbances. Co-administration of verapamil and ivabradine must be avoided.

Verapamil is a P-gp blocker and may increase exposure to the direct thrombin inhibitor dabigatran upon concurrent administration. Dose adjustments for dabigatran is not necessary in such cases.

Due to the nebivolol component, avoid concurrent use of nebivolol/valsartan (Byvalson) with the following: CYP2D6 inhibitors (quinidine, fluoxetine, paroxetine); other beta-blockers, digitalis, and calcium channel blockers.

Hydrochlorothiazide may potentiate the orthostatic effects of alcohol, barbiturates, or narcotics; interact with oral antidiabetic drugs and insulin requiring a dose adjustment of the antidiabetic agent; impair the absorption of HCTZ with anionic exchange resins (such as cholestyramine); intensify electrolyte depletion with corticosteroids; reduce lithium clearance; and lead to symptomatic hyponatremia with carbamazepine. NSAIDs can reduce diuretic, natriuretic, and antihypertensive effects of diuretics.

Amlodipine may increase the systemic exposure of cyclosporin or tacrolimus when administered together. Monitoring of trough blood levels of cyclosporin and tacrolimus is recommended and dosage adjustment may be needed.

No drug interaction studies have been conducted with amlodipine/valsartan (Exforge) or amlodipine/valsartan/HCTZ (Exforge HCT).

ADVERSE EFFECTS[52,53,54,55,56,57,58,59]

Drug	Cough	Headache	Dizziness	Edema
amlodipine (n=475)	0.4	2.9	2.3	5.1
benazepril (n=554)	1.8	3.8	1.6	0.9
amlodipine/benazepril (Lotrel) (n=760)	3.3	2.2	1.3	2.1
placebo (n=408)	0.2	5.6	1.5	2.2

Drug	Naso-pharyngitis	Headache	Fatigue	Peripheral Edema
amlodipine/olmesartan/HCTZ (Tribenzor) (n=574)	3.5	6.4	4.2	7.7
olmesartan/HCTZ (n=580)	3.4	6.6	5.3	1
amlodipine/olmesartan (n=596)	1.8	7	5.7	7
HCTZ/amlodipine (n=552)	2.9	6	6.5	8.3

Drug	Cough	Headache	Dizziness	Peripheral Edema
amlodipine (n=280)	0.7	2.9	1.1	13.2
perindopril (n=278)	2.9	2.9	1.4	0.4
amlodipine/perindopril (Prestalia) (n=279)	3.2	2.5	2.5	7.2

Drug	Back pain	Dizziness	Peripheral Edema	Other Edema
amlodipine/telmisartan (Twynsta) (n=789)	2.2	3	4.8	< 2
placebo (n=46)	0	2.2	0	nr

Drug	Naso-pharyngitis	URTI	Dizziness	Peripheral Edema
amlodipine/valsartan (Exforge) (n=1,437)	4.3	2.9	2.1	5.4
placebo (n=337)	1.8	2.1	0.9	3

Drug	Dyspepsia	Headache	Dizziness	Edema
amlodipine/valsartan/HCTZ (Exforge HCT) (n=582)	2.2	5.2	8.2	6.5
valsartan/HCTZ (n=559)	0.9	5.5	7.2	1.4
amlodipine/valsartan (n=566)	1.1	5.3	2.5	11.5
HCTZ/amlodipine (n=561)	0.4	7.1	4.1	11.2

Drug	Cough	Headache	Dizziness	Edema
verapamil SR/trandolapril (Tarka) (n=541)	4.6	8.9	3.1	1.3
placebo (n=206)	2.4	9.7	1.9	2.4

URTI = Upper Respiratory Tract Infection

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive.

The overall incidence of adverse reactions for amlodipine/olmesartan (Azor) was similar to that seen with corresponding doses of the individual components and to placebo.[60] Edema was the most frequently reported adverse effect (≥ 3%) in the amlodipine/olmesartan (Azor) group compared to placebo.

The overall incidence of reported adverse events on treatment with nebivolol/valsartan (Byvalson) was similar to placebo and its individual components.

SPECIAL POPULATIONS[61,62,63,64,65,66,67,68,69]

Pediatrics

Due to the fixed-dose combinations of this class, the Angiotensin Modulators Combinations class does not lend itself for use in pediatric patients. Safety and effectiveness in pediatric patients using the combination products have not been established.

Pregnancy

All products in this review are Pregnancy Category D and all products carry a boxed warning regarding fetal toxicity. When pregnancy is detected, discontinue medication as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Renal Impairment

Amlodipine/benazepril (Lotrel), amlodipine/olmesartan/HCTZ (Tribenzor), and amlodipine/valsartan/ HCTZ (Exforge HCT) are not recommended in patients with creatinine clearance (CrCL) < 30 mL/min.

Amlodipine/perindopril (Prestalia) is not recommended in patients with CrCl< 60 mL/min.

There have been no studies of amlodipine/olmesartan (Azor) in patients with renal impairment; there are no specific dosage adjustment recommendations. No initial dose adjustment for amlodipine/telmisartan (Twynsta) is required in patients with mild to moderate renal impairment; however, doses should be titrated slowly in patients with severe renal impairment.

Use caution with amlodipine/valsartan (Exforge) when CrCl < 10 mL/min; although it has not been studied in severe renal impairment.

Verapamil SR/trandolapril (Tarka) should be dose adjusted if CrCl < 30 mL/min.

Nebivolol/valsartan (Byvalson) is not recommended as initial treatment in patients with severe renal impairment because the appropriate starting dose of nebivolol in such patients would be 2.5 mg once a day which is lower than the nebivolol dose of 5 mg contained in this fixed-dose combination. Safety and effectiveness of this combination in patients with moderate impairment has not been studied. No dosage adjustment is required with mild impairment.

Hepatic Impairment

Patients with hepatic impairment have decreased clearance of amlodipine and verapamil. Caution should be exercised when utilizing amlodipine-containing (Lotrel, Azor, Tribenzor, Twynsta, Exforge, Exforge HCT) or verapamil-containing (Tarka) products in patients with hepatic impairment. Amlodipine should be started at a dose of 2.5 mg and titrated slowly in this patient population. This strength is not an option with the combination products: Azor, Exforge, Exforge HCT, Tribenzor, or

Twynsta. A dosage adjustment may be required for verapamil SR/trandolapril (Tarka) in patients with hepatic impairment.

Amlodipine/perindopril (Prestalia) is not recommended in patients with hepatic impairment. Nebivolol/valsartan (Byvalson) is contraindicated in patients with severe (Child-Pugh > B) hepatic impairment; it's use is not recommended in patients with moderate impairment because the recommended starting dose of nebivolol is 2.5 mg once daily, which is not available.

Other Populations

African American patients receiving ACE inhibitor monotherapy have reported a higher incidence of angioedema compared to non-African Americans. In controlled clinical trials, ACE inhibitors have less effect on blood pressure in African American patients than in non-African Americans.[70] Amlodipine/olmesartan (Azor) and amlodipine/olmesartan/HCTZ (Tribenzor) have shown to be effective in treating African American patients, with the magnitude of blood pressure reduction in African Americans approaching that observed in the non-African Americans population.

When starting or adding amlodipine for patients at least 75 years old or patients with hepatic impairment, the recommended dose of amlodipine is 2.5 mg due to impaired clearance.

DOSAGES[71,72,73,74,75,76,77,78,79]

Drug	Dosage	Combinations Available (Calcium Channel Blocker/Angiotensin Modulator)
amlodipine/benazepril (Lotrel)	1 daily	2.5/10 mg, 5/10 mg, 5/20 mg, 10/20 mg, 5/40 mg, 10/40 mg capsules
amlodipine/olmesartan (Azor)	1 daily	5/20 mg, 5/40 mg, 10/20 mg, 10/40 mg tablets
amlodipine/olmesartan/HCTZ (Tribenzor)	1 daily	5/20/12.5 mg, 5/40 /12.5 mg, 5/40/25 mg, 10/40/12.5 mg, 10/40/25 mg tablets
amlodipine/perindopril (Prestalia)	1 daily	3.5/2.5 mg, 7/5 mg, 14/10 mg tablets
amlodipine/telmisartan (Twynsta)	1 daily	5/40 mg, 10/40 mg, 5/80 mg, 10/80 mg tablets
amlodipine/valsartan (Exforge)	1 daily	5/160 mg, 10/160 mg, 5/320 mg, 10/320 mg tablets
amlodipine/valsartan/HCTZ (Exforge HCT)	1 daily	5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, 10/320/25 mg tablets
nebivolol/valsartan (Byvalson)	1 daily	5/80 mg tablets
verapamil SR/trandolapril (Tarka)	1 daily	240/1 mg, 180/2 mg, 240/2 mg, 240/4 mg tablets

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in the commercially available combinations for this category. Randomized, controlled trials comparing agents within this class for the treatment of hypertension are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis

techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

amlodipine/benazepril (Lotrel) and amlodipine (Norvasc) and/or benazepril (Lotensin)

In a multicenter, randomized, double-blind study, 448 patients were randomized to receive 1 of the following treatments for 8 weeks: 1) benazepril 10 mg plus placebo, 2) benazepril 10 mg plus amlodipine 2.5 mg, or 3) benazepril 10 mg plus amlodipine 5 mg.[80] Initially, patients underwent a 2-week placebo run-in phase followed by a 4-week benazepril 10 mg daily run-in phase and then underwent randomization if the mean diastolic blood pressure (DBP) was ≥ 95 mm Hg and < 120 mm Hg after 4 weeks of benazepril 10 mg daily. The 24-hour post-dose sitting and standing systolic BP (SBP) and DBP values were statistically lower with combination therapy than with benazepril 10 mg. The tolerability was good in the 3 treatment groups.

In a multicenter, double-blind, parallel-group study, 308 patients were randomized to 1 of the following treatments for 8 weeks: amlodipine 5 mg/benazepril 20 mg, amlodipine 5 mg, benazepril 20 mg, or placebo once daily for the treatment of hypertension.[81] The combination had a significantly greater reduction in blood pressure compared to the other monotherapies ($p<0.001$). A responder rate, as defined as DBP < 90 mm Hg or > 10 mm Hg decrease in mean sitting DBP, of 87% was observed for amlodipine/benazepril versus 67.5% for amlodipine, 53.3% for benazepril, and 15.8% for placebo ($p<0.005$). Edema occurred less often in the amlodipine/benazepril group than in the amlodipine group which has also been observed in other studies.[82]

A double-blind study compared the efficacy and safety of amlodipine 5 to 10 mg and benazepril 40 mg to benazepril 40 mg monotherapy in hypertensive patients (n=298) not controlled on benazepril 40 mg monotherapy.[83] Patients underwent a 2-week washout period and then started on benazepril 40 mg daily. Patients with a mean sitting DBP ≥ 95 mm Hg were randomized to amlodipine 5 mg (then amlodipine 10 mg after 4 weeks) in addition to benazepril 40 mg or to continue on benazepril 40 mg daily for 8 weeks. The mean reduction in sitting BP after 8 weeks compared to baseline was -5/-7 mm Hg with benazepril and -17/-14 mm Hg with amlodipine/benazepril ($p<0.0001$). Goal attainment of target BP (DBP < 90 mm Hg) was achieved in 80% and 45% of amlodipine/benazepril and benazepril groups, respectively ($p<0.0001$). Both therapies were well tolerated.

A total of 364 patients with stage 2 hypertension were enrolled in a multicenter, double-blind, 12-week trial comparing the efficacy of amlodipine/benazepril combination and amlodipine monotherapy.[84] Patients were randomized to amlodipine/benazepril 5/20 mg daily and titrated to 10/20 mg daily or amlodipine 5 mg daily titrated to 10 mg daily. The combination therapy achieved a reduction in SBP of greater than -25 to -32 mm Hg in 74.2% of patients whereas, in the amlodipine group, only 53.9% of patients achieved the desired BP reductions ($p<0.0001$). Significantly more patients in the combination therapy group attained BP < 140/90 mm Hg (61%) compared to 43.3% in the monotherapy group ($p=0.0007$). A significant difference was also seen for those patients achieving a BP < 135/80 mm Hg (35.7% versus 19.1% of patients, respectively; $p=0.0004$). For patients with baseline SBP > 180 mm Hg, combination therapy had significantly greater reductions in SBP compared to monotherapy (-42.3 versus -30.4 mm Hg, $p=0.001$). Another study, SELECT, has been published with similar results.[85]

In a randomized, double-blind, multicenter, 12-week study, 70 hypertensive patients with at least 1 other endothelial dysfunction risk factor were assigned to amlodipine/benazepril 5/20 mg per day (force titrated to 5/40 mg per day) or amlodipine 5 mg per day (force titrated to 10 mg per day).[86] The study examined combination therapy versus monotherapy in modulating endothelial dysfunction. Both treatment arms resulted in significant median increases from baseline in percentage flow-mediated vasodilation (2% versus 1.2%, respectively), but between group differences were not statistically significant. Reductions in SBP (p=0.0452) and DBP (p=0.0297) were significantly greater with the combination therapy (-18.6/-12.3 mm Hg) versus monotherapy (-14.8/-9.1 mm Hg). A correlation between reduction in SBP and change in percentage of flow mediated vasodilation was seen only for combination therapy.

Amlodipine and benazepril were compared to each other and to the combination in a randomized, double-blind, placebo-controlled, multicenter trial.[87] A total of 454 adult patients with hypertension were randomized to amlodipine 5 mg, benazepril 10 mg, the combination, or placebo once daily for 8 weeks. The combination group had greater reductions in sitting DBP from baseline compared to amlodipine (p<0.03), benazepril, and placebo (both p<0.001). Heart rate did not differ among the groups. Edema was less in the combination group compared to amlodipine (1.7 versus 4.5%).

In a multicenter, double-blind, 8-week study, 111 Chinese patients with mild to moderate hypertension were randomized to amlodipine/benazepril 2.5/5 mg daily or amlodipine 5 mg daily.[88] Blood pressure was obtained after 4 weeks of therapy and then the dose was titrated up if BP was > 140/90 mm Hg. After 8 weeks of therapy, BP control rates were similar with 56% in the combination group and 46.2% in the amlodipine monotherapy group (p=0.32). Fixed-dose combination resulted in similar reductions in sitting SBP and DBP compared with monotherapy (SBP: -19.3 mm Hg versus -20.9 mm Hg; DBP: -9.2 mm Hg versus -11.3 mm Hg; both p=NS). Safety profiles did not differ between groups, but cough was more common in the combination group (11% versus 0%; p=0.013).

amlodipine/olmesartan (Azor) versus olmesartan initial therapy

A randomized, double-blind, parallel-group, multicenter trial included patients with moderate to severe hypertension (≥ 160/100 mm Hg) and investigated the additional efficacy on BP reduction and BP goal rates (< 140/90 mm Hg for patients without diabetes mellitus, < 130/80 mm Hg for patients with diabetes) when amlodipine 5 or 10 mg per day was added to olmesartan 20 mg/day in patients not adequately controlled on olmesartan alone.[89] After an 8-week open-label olmesartan 20 mg monotherapy period, 538 patients with BP ≥ 140/90 mm Hg were randomized to 8 weeks of olmesartan/placebo, olmesartan/amlodipine 20 mg/5 mg, or olmesartan/amlodipine 20 mg/10 mg. The adjusted mean change in seated DBP (SeDBP) from baseline was -7.6 mm Hg for olmesartan/placebo, -10.4 mm Hg for olmesartan/amlodipine 20 mg/5 mg (p=0.0006 versus olmesartan/placebo), and -10.9 mm Hg for olmesartan/amlodipine 20 mg/10 mg (p<0.0001 versus olmesartan/placebo). Mean changes in seated SBP (SeSBP) from baseline with olmesartan/placebo, olmesartan/amlodipine 20 mg/5 mg, and olmesartan/amlodipine 20 mg/10 mg were -10.8, -16.1, and -16.7 mm Hg, respectively (p<0.0001 for both dose regimens versus olmesartan/placebo). BP goal rates were higher with olmesartan/amlodipine 20 mg/5 mg and olmesartan/amlodipine 20 mg/10 mg (44.5% and 45.8%, respectively; p=0.0011 and p=0.0004, respectively) versus olmesartan/placebo (28.5%). Combination therapy was well tolerated, and the incidence of drug-related adverse events

was 8.9% for olmesartan/placebo, 7.7% for olmesartan/amlodipine 20 mg/5 mg, and 11.3% for olmesartan/amlodipine 20 mg/10 mg (p=0.49).

amlodipine/olmesartan (Azor) versus amlodipine (Norvasc) or olmesartan (Benicar)

In a multicenter, randomized, double-blind trial, the efficacy and tolerability of the combination of olmesartan and amlodipine were compared to the individual components in 1,940 patients with hypertension.[90] Patients were either untreated or underwent a 2-week wash-out period and had a seated DBP of 95 – 120 mm Hg. The mean baseline BP was 164/102 mm Hg, and 79.3% of patients had stage 2 hypertension. Patients were randomized to olmesartan 10, 20, or 40 mg daily, amlodipine 5 or 10 mg daily, each possible combination of amlodipine/olmesartan, or placebo. The primary endpoint was the change from baseline in seated DBP after eight weeks of treatment. Combination therapy with amlodipine/olmesartan had dose-dependent reductions in seated DBP ranging from -13.8 mm Hg to -19 mm Hg. The secondary endpoint, seated SBP, reductions observed in the combination therapy group ranged from -23.6 mm Hg to -30.1 mm Hg. Both SBP and DBP reductions with the combination therapy were significantly greater than those observed with either monotherapy (p<0.001). The percentages of patients achieving BP goal attainment were significantly higher with combination therapy compared to monotherapy (p<0.005). Combination therapy was well tolerated. The most common adverse events were edema and headache. Percentages for edema ranged from 9.9% with olmesartan 20 mg to 36.8% with amlodipine 10 mg compared to 12.3% with placebo. Percentages of patients reporting headache ranged from 2.5% in the amlodipine/olmesartan 10-5 mg group to 8.7% in the olmesartan 20 mg group; a total of 14.2% of patients receiving placebo reported headache.

amlodipine/olmesartan/HCTZ (Tribenzor) versus amlodipine (Norvasc) or olmesartan (Benicar)

The antihypertensive efficacy of triple combination therapy with amlodipine/olmesartan/HCTZ was studied in a double-blind, active-controlled study in hypertensive patients (n=2,492).[91] Patients were randomized to receive olmesartan/amlodipine/HCTZ 40/10/25 mg, olmesartan/amlodipine 40/10 mg, olmesartan/HCTZ 40/25 mg, or amlodipine/HCTZ 10/25 mg for 2 to 4 weeks. Patients were then randomized to continue on the dual therapy they were receiving or to receive triple therapy. After 8 weeks of treatment, the triple combination therapy produced greater reductions in both systolic and diastolic blood pressures (p<0.0001) compared to each of the dual combination therapies. Reductions in seated blood pressure measures were: 8.4/4.5 mm Hg for HCTZ 25 mg added to olmesartan 40 mg/amlodipine 10 mg; 7.6/5.4 mm Hg for amlodipine 10 mg added to olmesartan 40 mg/HCTZ 25 mg; and 8.1/5.4 mm Hg for olmesartan 40 mg added to amlodipine 10 mg/HCTZ 25 mg. A total of 440 patients participated in the ambulatory blood pressure monitoring portion of the study. Over the 24-hour period, there was a greater reduction in diastolic and systolic ambulatory blood pressure for olmesartan/amlodipine/hydrochlorothiazide 40/10/25 mg compared to each of the dual combination therapies.

amlodipine/perindopril arginine (Prestalia) versus amlodipine (Norvasc) or perindopril erbumine (Aceon)

In a double-blind, active controlled study a total of 837 hypertensive patients with a mean baseline blood pressure of 158/101 mmHg received either the highest strength of amlodipine/perindopril arginine 10/14 mg, perindopril erbumine 16 mg, or amlodipine 10 mg once daily for 6 weeks.[92] Overall,

20% of the population had type 2 diabetes and 34% were African American. At Week 6, amlodipine/perindopril arginine 10/14 mg resulted in statistically significantly greater reductions in blood pressure than each monotherapy. The reductions in blood pressure with the combination product were 10.1/6.3 mmHg greater than with perindopril erbumine 16 mg and 3.9/2.5 mmHg greater than with amlodipine 10 mg. Treatment with amlodipine/perindopril arginine 10/14 mg did not provide additional blood pressure reductions beyond that achieved with use of amlodipine 10 mg in African American patients and in diabetic patients.

The lowest strength of amlodipine/perindopril arginine was studied in 246 hypertensive patients with a mean baseline blood pressure of 161/101 mmHg.[93] Patients received amlodipine/perindopril arginine 2.5 /3.5 mg, perindopril arginine 3.5 mg, perindopril arginine 5 mg, amlodipine 2.5 mg, amlodipine 5 mg, or placebo. No patients in the study had diabetes and 1% was African American. At Week 8, amlodipine/perindopril arginine 2.5 /3.5 mg resulted in statistically significantly greater reductions in blood pressure than perindopril arginine 3.5 mg and amlodipine 2.5 mg. The reduction in blood pressure with amlodipine/perindopril arginine 2.5 /3.5 mg was 7.2/4.1 mmHg greater than with placebo.

amlodipine/telmisartan (Twynsta) versus amlodipine (Norvasc) or telmisartan (Micardis)

A randomized 4 x 4 factorial study evaluated the efficacy and safety of telmisartan plus amlodipine in 1,461 patients with stage 1 or 2 hypertension (BP 153.2 ± 12.1/101.7 ± 4.3 mm Hg).[94] Patients were randomized to one of 16 treatment groups using combinations of dose ranges of telmisartan 0 to 80 mg and amlodipine of 0 to 10 mg daily for 8 weeks. Blood pressure reductions were greater with combination therapy than respective monotherapies, with the greatest mean systolic/diastolic BP reductions seen in the telmisartan 80 mg plus amlodipine 10 mg group (-26.4/-20.1 mm Hg; $p<0.05$ compared with both monotherapies). BP control was also greatest in the telmisartan 80 mg/amlodipine 10 mg group (76.5% [overall control] and 85.3% [DBP control]), and BP response rates were more than 90% with this combination. Peripheral edema was most common in the amlodipine 10 mg group (17.8%); however, this rate was notably lower when amlodipine was used in combination with telmisartan: 11.4% (telmisartan 20 mg/amlodipine 10 mg), 6.2% (telmisartan 40 mg/ amlodipine 10 mg, and 11.3% (telmisartan 80 mg/amlodipine 10 mg).

A placebo-controlled, double-blind, 4 x 4 factorial design trial in 562 patients with clinic diastolic BP at least 95 and 119 mm Hg or less were randomized to receive telmisartan 0, 20, 40, or 80 mg and/or amlodipine 0, 2.5, 5, or 10 mg.[95] Ambulatory BP monitoring was performed at baseline and after 8 weeks of treatment; the endpoints of interest were the changes from baseline in 24-h systolic and diastolic BP. Secondary endpoints included the proportion of responders (≥ 10 mm Hg BP reduction from baseline and/or < 130/80 mm Hg mean 24-h BP) and controlled patients (< 130/80 mm Hg mean 24-h BP). Combination therapies of telmisartan and amlodipine lowered 24-h BP to a larger extent than the corresponding monotherapies at all doses. Mean reductions from baseline in 24-h BP for the combination of the highest doses of telmisartan 80 mg and amlodipine 10 mg were -22.4/-14.6 mm Hg versus -11.9/-6.9 mm Hg for amlodipine 10 mg and -11/-6.9 mm Hg for telmisartan 80 mg ($p<0.0001$ for each comparison). In addition, BP response and control rates (24-h BP < 130/80 mm Hg) were significantly higher with the combination therapy versus the monotherapy groups.

Patients (n=1,078) with a DBP ≥ 100 mm Hg at baseline were included in a subgroup analysis of the above study.[96] The primary endpoint was the change in the in-clinic seated trough cuff DBP from baseline to study end for combination versus respective monotherapies. Secondary endpoints included the change in the in-clinic seated trough SBP, BP response, and control rates. In-clinic DBP and SBP reductions were greater with combination therapies than respective monotherapies, with the greatest least-square mean SBP/DBP reductions (-26.5 ± 1.2/-21 ± 0.8 mm Hg) observed in the telmisartan 80 mg plus amlodipine 10 mg group; 77% and 85% of patients in this treatment group achieved BP control (< 140/90 mm Hg) and DBP control (< 90 mm Hg), respectively. Peripheral edema was reported in 17.2% of patients in the amlodipine 10 mg group; however, this was substantially lower when telmisartan was used in combination: 7% (telmisartan 40 mg/amlodipine 10 mg) and 9.5% (telmisartan 80 mg/ amlodipine 10 mg).

amlodipine/valsartan (Exforge) versus amlodipine (Norvasc) or valsartan (Diovan)

Efficacy of the combination of amlodipine and valsartan were compared to the individual components in 2 multicenter, 8-week, randomized, double-blind, parallel-group trials.[97] In the first study, 1,911 patients were randomized to receive amlodipine 2.5 or 5 mg once daily, valsartan 40 to 320 mg once daily, or the combination of amlodipine 2.5 or 5 mg plus valsartan 40 to 320 mg once daily, or placebo for 8 weeks. In the second study, 1,250 patients were randomized to amlodipine 10 mg once daily, valsartan 160 or 320 mg once daily, or the combination of amlodipine 10 mg with valsartan 160 or 320 mg once daily, or placebo for 8 weeks. The primary efficacy parameter was the change from baseline in mean sitting DBP at the end of the study. A positive dose response was observed for all combinations. With the exception of a few combinations that included amlodipine 2.5 mg, the combination regimens in both studies were associated with significantly greater reductions in mean sitting DBP and mean sitting SBP compared with their individual components and placebo ($p<0.05$). The highest response rate, defined as patients achieving mean sitting DBP < 90 mm Hg or > 10 mm Hg decrease from baseline, in the first study was associated with the highest dose of combination therapy (amlodipine 5 mg/valsartan 320 mg: 91.3%). Amlodipine 5 mg, valsartan 320 mg, and placebo were associated with response rates of 71.9%, 73.4%, and 40.9%, respectively. In the second study, the response rates were similar for the 2 doses of combination therapy (amlodipine 10 mg/valsartan 160 mg: 88.5%; amlodipine 10 mg/valsartan 320 mg: 87.5%). Amlodipine 10 mg was associated with a response rate of 86.9%; valsartan 160 and 320 mg were associated with response rates of 74.9% and 72%, respectively; and placebo was associated with a response rate of 49.3%. Peripheral edema was reported less frequently with the combination therapy than with amlodipine monotherapy (5.4% versus 8.7%, respectively; $p=0.014$). Combination therapy had a significantly higher incidence of peripheral edema compared to valsartan monotherapy (5.4% versus 2.1%, respectively; $p<0.001$) but not significantly different than placebo (3%).

amlodipine/valsartan (Exforge)

In a randomized, double-blind, multicenter study, 894 patients whose blood pressure was uncontrolled by monotherapy were switched to amlodipine/valsartan 5/160 mg or 10/160 mg.[98] After 16 weeks, BP control (BP < 140/90 mm Hg or < 130/80 mm Hg for diabetics) was achieved in 72.7% (95% CI, 68.6 to 76.9) of patients receiving amlodipine/valsartan 5/160 mg and in 74.8% (95% CI, 70.8 to 78.9) receiving amlodipine/valsartan 10/160 mg. Incremental reductions from baseline in mean sitting systolic and diastolic BP were significantly greater with the higher dose (20+/-0.7 versus 17.5 ± 0.7 mm Hg,

p=0.0003 and 11.6 ± 0.4 versus 10.4 ± 0.4 mm Hg, p=0.0046). Peripheral edema was the most frequent adverse event.

A multicenter, randomized, double-blind, active-controlled study in patients with essential hypertension was conducted to demonstrate additional BP-lowering effects of amlodipine/valsartan combination in patients whose BP was not adequately controlled on valsartan alone.[99] After a washout period followed by a single-blind valsartan 160 mg run-in period, patients with mean sitting DBP ≥ 90 mm Hg and < 110 mm Hg were randomized to receive amlodipine/valsartan (10/160 mg or 5/160 mg) or valsartan 160 mg for 8 weeks. The primary efficacy variable was change from baseline in mean DBP at study end. Secondary efficacy variables included change from baseline in mean sitting SBP, responder rate (mean DBP < 90 mm Hg or ≥ 10 mm Hg reduction from baseline), and DBP control rate (mean DBP < 90 mm Hg). Of 1,136 patients enrolled in the single-blind phase, 947 (mean age: 54.6 years) were randomized. Greater reductions in mean SBP/DBP were observed in both amlodipine/valsartan combinations (10/160 mg: 14.3/11.5 mm Hg, 5/160 mg: 12.2/9.6 mm Hg; both p<0.0001) compared to valsartan 160 mg (8.3/6.7 mm Hg). Responder rates were higher in both combination therapy groups (10/160 mg: 81% [p<0.0001]; 5/160 mg: 68% [p=0.0018], respectively) compared to monotherapy (57%). Peripheral edema was the most frequent adverse event reported in amlodipine/valsartan 10/160 mg (9.1%), 5/160 mg (0.9%), and valsartan 160 mg (1.3%).

amlodipine/valsartan (Exforge) versus amlodipine as initial therapy

Two double-blind, active-controlled studies were conducted in which the combination of amlodipine/valsartan was administered as initial therapy.[100] In one study, a total of 572 African American patients with moderate to severe hypertension were randomized to receive either combination amlodipine/valsartan or amlodipine monotherapy for 12 weeks. The initial dose of amlodipine/valsartan was 5/160 mg for 2 weeks with forced titration to 10/160 mg for 2 weeks, followed by optional titration to 10/320 mg for four weeks and optional addition of HCTZ 12.5 mg for 4 weeks. The initial dose of amlodipine was 5 mg for 2 weeks with forced titration to 10 mg for 2 weeks, followed by optional titration to 10 mg for 4 weeks and optional addition of HCTZ 12.5 mg for 4 weeks. At the primary endpoint of 8 weeks, the treatment difference between amlodipine/valsartan and amlodipine was 6.7/2.8 mm Hg in favor of the combination product.

In the other study of similar design, a total of 646 patients with moderate to severe hypertension (SBP of ≥ 160 mm Hg and < 200 mm Hg) were randomized to receive either combination amlodipine/valsartan or amlodipine monotherapy for 8 weeks.[101] The initial dose of amlodipine/valsartan was 5/160 mg for 2 weeks with forced titration to 10/160 mg for 2 weeks, followed by the optional addition of HCTZ 12.5 mg for 4 weeks. The initial dose of amlodipine was 5 mg for 2 weeks with forced titration to 10 mg for 2 weeks followed by the optional addition of HCTZ 12.5 mg for 4 weeks. At the primary endpoint of 4 weeks, the treatment difference between amlodipine/valsartan and amlodipine was 6.6/3.9 mm Hg in favor of the combination product.

This multicenter, randomized, double-blind, active-controlled study evaluated the efficacy and tolerability of amlodipine/valsartan combination therapy in patients with essential hypertension (n=944) who were not adequately controlled on amlodipine monotherapy.[102] Patients with mean sitting diastolic blood pressure (msDBP) ≥ 90 mm Hg and < 110 mm Hg were randomized to receive amlodipine/valsartan 10/160 mg (n=473) or amlodipine 10 mg (n=471) for 8 weeks after a washout period followed by a single-blind amlodipine 10 mg run-in period. The primary efficacy variable was change from baseline in msDBP at study endpoint. Secondary endpoints were change from baseline in

mean sitting systolic blood pressure (msSBP), responder rate (msDBP < 90 mm Hg or ≥ 10 mm Hg reduction from baseline), and DBP control rate (msDBP < 90 mm Hg). Combination therapy resulted in greater reductions (p<0.0001) from baseline in msSBP/msDBP (12.9/11.4 mm Hg) compared to monotherapy (10/9.3 mm Hg). Responder rate was significantly greater (p=0.0011) with combination therapy (79%) compared to monotherapy (70.1%), and the percentage of patients with controlled DBP was also higher (p<0.0001) with combination therapy (77.8%) compared to monotherapy (66.5%). The incidence of peripheral edema was slightly higher with amlodipine monotherapy (9.4%) compared to combination therapy (7.6%).

nebivolol/valsartan (Byvalson) and nebivolol (Bystolic) or valsartan (Diovan) or placebo

In a phase 3, double-blind, placebo-controlled, dose-escalating, 8-week study (n = 4,161), patients with Stage 1 or 2 hypertension were randomized to 1 of 8 treatment groups including: 3 fixed-dose combinations of nebivolol and valsartan (5/80 mg, 5/160 mg, 10/160 mg), nebivolol monotherapy (5 mg, 20 mg), valsartan monotherapy (80 mg, 160 mg), or placebo.[103] Mean baseline SBP was 155 mm Hg and mean baseline DBP was 100 mm Hg. All doses were doubled after 4 weeks of initial treatment to 10/160 mg, 10/320 mg, and 20/ 320 mg in the fixed-dose groups, 10 mg and 40 mg in the nebivolol monotherapy groups, and 160 mg and 320 mg in the valsartan monotherapy groups. Initial therapy with nebivolol/valsartan 5/80 mg for 4 weeks resulted in placebo-adjusted reductions from baseline in both SBP and DBP of -8.3 and -7.2 mmHg, respectively. The results of this pivotal study revealed that treatment with nebivolol/valsartan 5/80 mg resulted in greater reductions in SBP and DBP as compared with treatment with nebivolol 5 mg alone (p<0.0001 for both SBP and DBP) or valsartan 80 mg alone (p=0.0007 for SBP and p<0.0001 for DBP). The overall rate of adverse events was similar across treatment groups and placebo during this 4 week period. Nebivolol/valsartan in tablet strengths of 5/160 mg and 10g/160 mg are not available in the US.

verapamil SR/trandolapril (Tarka) and trandolapril (Mavik) and/or verapamil SR

In a randomized, double-blind placebo-controlled trial, trandolapril, verapamil SR, the combination of the 2 agents, and placebo were evaluated for antihypertensive efficacy in 631 adults with hypertension.[104] Both single agent groups lowered BP more than placebo. The combination lowered BP more than either agent alone. All groups had similar adverse events, and therapies were well tolerated. Two other prospective, double-blind trials found similar results.[105,106]

The antihypertensive efficacy of verapamil SR and trandolapril were evaluated in 438 patients with high normal BP or borderline isolated systolic hypertension and type 2 diabetes.[107] The patients were randomized to verapamil SR plus trandolapril, trandolapril, or placebo and followed for 16 weeks in a double-blind fashion. Doses were doubled if BP goals were not achieved after 8 weeks (<130/85 mm Hg). Both active treatment groups significantly lowered BP compared to placebo (both p<0.001). However, no significant difference in the control of SBP was seen between the 2 active treatment groups. The percentage of patients achieving BP < 130/85 mm Hg was 36.5% in the trandolapril group, 37.8% in the combination group, and 14.9% in the placebo group (p=0.009, combination and trandolapril groups versus placebo). Control rate for DBP (< 85 mm Hg) was significantly higher in the combination group (88.8%) when compared with trandolapril (79.1%) or placebo (63.5%; p=0.002). Withdrawal rates were similar in all groups.

The BENEDICT study assessed trandolapril and verapamil, alone or in combination, for efficacy in preventing microalbuminuria in 1,204 patients with hypertension, type 2 diabetes, and normal urinary albumin excretion.[108] Patients were randomized to 3 years of trandolapril 2 mg daily plus verapamil SR 180 mg daily, trandolapril 2 mg daily, verapamil SR 240 mg daily, or placebo in a double-blind fashion. The primary outcome was the development of microalbuminuria (>20 mcg/min at 2 visits). Microalbuminuria was observed in 5.7% of the combination group, 6% in trandolapril monotherapy, 11.9% in verapamil monotherapy, and 10% in the placebo group. Trandolapril plus verapamil and trandolapril monotherapy reduced the risk of the development of microalbuminuria to a similar extent and greater than placebo. Verapamil was similar to placebo.

The INVEST trial compared the combination of verapamil SR and trandolapril with atenolol and hydrochlorothiazide in 22,576 hypertensive coronary artery disease (CAD) patients over 50 years old.[109] In the randomized, open-label, blinded endpoint, multinational trial, patients were randomized to verapamil SR or atenolol. After a mean follow-up of 2.7 years, the occurrence of all-cause death, nonfatal myocardial infarction (MI) or nonfatal stroke, and BP control and goal attainment were similar in both groups. While the study did not specifically provide the combination tablet form of verapamil SR and trandolapril, INVEST did provide efficacy information regarding the co-administration of verapamil SR and trandolapril in a large clinical trial.

A subgroup of patients without diabetes from the randomized, double-blinded INVEST trial at study entry were investigated for newly diagnosed diabetes during follow-up.[110] Newly diagnosed diabetes was less frequent in the verapamil SR versus atenolol group (7% versus 8.2%; hazard ratio [HR] 0.85; 95% CI, 0.76 to 0.95; p<0.01). Some of the characteristics of risk for newly diagnosed diabetes included United States residence, left ventricular hypertrophy, previous stroke/transient ischemic attack, and Hispanic ethnicity. Addition of trandolapril to verapamil SR decreased diabetes risk and addition of hydrochlorothiazide to atenolol increased the diabetes risk.

Another substudy of INVEST evaluated 7,218 patients with prior MI for the primary outcome of time to first occurrence of death (all-cause), nonfatal MI, or nonfatal stroke.[111] Secondary outcomes included death, total MI (fatal and nonfatal), and total stroke (fatal and nonfatal) considered separately. During the 2.8 ± 1 years of follow-up, patients assigned to the verapamil-SR-based and atenolol-based groups had comparable blood pressure control, and the incidence of the primary outcome was equivalent. There was no difference between the 2 groups for the outcomes of either death or total MI. More patients reported excellent/good well-being (82.3% versus 78%, p=0.02) at 24 months with a trend toward less incidence of angina pectoris (12% versus 14.3%, adjusted p=0.07), nonfatal stroke (1.4% versus 2%; p=0.06), and total stroke (2% versus 2.5%, p=0.18) in the verapamil-SR-based group. In this study of hypertensive patients with prior MI, a verapamil SR-based group was equivalent to a beta-blocker-based group for blood pressure control and prevention of cardiovascular events.

META-ANALYSIS

A meta-analysis of 17 randomized controlled trials including 3,291 patients found that the combination treatment of amlodipine and ACE inhibitors resulted in a greater reduction of both systolic blood pressure (SBP) (weighted mean difference [WMD], 5.72; 95% CI, 4.1 to 7.33) and diastolic blood pressure (DBP) (WMD, 3.62; 95% CI, 4.85 to 2.39) than monotherapy.[112] The combination treatment also generated significantly greater reductions for the mean ambulatory SBP and DBP during the full 24 hours (WMD: SBP, 4.24 [95% CI, 6.82 to 1.67]; DBP, 2.23 [95% CI, 3.73 to 0.69]), but not for the trough

(WMD: SBP, 4.52, [95% CI, 9.56 to -0.51]; DBP, 3.7, [95% CI, 7.65 to -0.25]). The hypertension therapeutic control (SBP < 140 mm Hg, DBP < 90 mm Hg) rate for the combination treatment is higher than that for monotherapy (relative risk [RR], 1.36; 95% CI, 1.07 to 1.73). The combination treatment also resulted in a lower overall rate of adverse events (RR, 0.86; 95% CI, 0.75 to 0.99) and edema (RR, 0.4; 95% CI, 0.29 to 0.56), but a higher rate of cough (RR, 3.28; 95% CI, 2.03 to 5.29) as compared with monotherapy.

SUMMARY

Most patients require more than 1 medication to achieve adequate blood pressure control. The combinations of an angiotensin modulator with a calcium channel blocker or a beta blocker have been shown to be more effective than either agent alone for the treatment of hypertension. The combination products appear similar in efficacy and safety; however, comparative trials are lacking.

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